Metabolic dysfunction-associated fatty liver disease (MAFLD) and non-alcoholic fatty liver disease (NAFLD): distinct fatty liver entities with different clinical outcomes?

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In 2019, metabolic dysfunction-associated fatty liver disease (MAFLD) was introduced as a novel definition in order to represent the causal etiologies (i.e., overweight, type 2 diabetes, metabolic syndrome) of the majority of patients with fatty liver disease without discrimination for chronic alcohol consumption, as non-alcoholic fatty liver disease (NAFLD) became the leading cause of chronic injury in western societies (1). NAFLD diagnosis is based on the detection of hepatic steatosis with exclusion of any secondary causality, especially chronic harmful alcohol ingestion. Unlike NAFLD, MAFLD definition requires invasive or non-invasive hepatic steatosis assessment in addition to being overweight/obese, and/or type 2 diabetes and/or the presence of two metabolic dysfunction criteria without the exclusion of other liver diseases. Therefore, MAFLD and NAFLD do not reflect the same patient population. While MAFLD includes any patient with relevant metabolic risk factors and steatosis regardless of additional causes, NAFLD includes a significant number of patients without metabolic risk factors (lean NAFLD). However, to date there is little data available on the impact of the modified definition on clinical outcome and associated mortality, as previously discussed elsewhere (2).

With great interest we read the original article by Kim et al. focusing on the differences between MAFLD and NAFLD regarding cardiovascular, cancer-related, and all-cause mortality (3). Unfortunately, the authors did not have access to liver-related mortality data nor differentiate into different cancer types (i.e., hepatic vs. extrahepatic). However, in a nested analysis of the NHANES III cohort, representing 7,761 individuals, Kim et al. clearly demonstrated that MAFLD was associated with significantly higher all-cause mortality (HR =1.17; 95% CI: 1.04–1.32). In contrast, individuals that were declared as NAFLD following ultrasound diagnosis of steatosis and exclusion of harmful alcohol intake and viral hepatitis B or C had no significant increase in all-cause mortality after multivariate analysis and adjustment for metabolic risk factors. Indeed, advanced fibrosis in MAFLD, as estimated by NAFLD fibrosis score, FIB-4 or APRI resulted in an even higher risk for all-cause mortality (HR =2.0; 95% CI: 1.49–2.69), while in NAFLD, individuals with advanced fibrosis remained at a non-significant level of all-cause mortality (HR =1.45; 95% CI: 0.95–2.21). Looking at specific causes, cancer-related mortality was associated with MAFLD (HR =1.95; 95% CI: 1.05–3.62), but not with NAFLD.

A recent meta-analysis revealed that MAFLD and NAFLD overlapped at a rate of 81.59% (CI: 66.51–

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90.82%), which is in line with the observations of Kim et al. (4). Here, MAFLD, compared to NAFLD was also associated with advanced stages of fibrosis, transaminase levels and metabolic dysfunction, which might be explained by the fact that MAFLD compared to NAFLD does not exclude other liver diseases (i.e., ALD, hepatitis B and C). As a closer association of fibrosis with MAFLD compared to NAFLD has been observed by other authors before, some authors even claim this definition to be more suitable for the detection of fibrosis in fatty liver disease (5). However, when addressing this issue, one would have to keep in mind that we are dealing with two different disease entities, that do not overlap in up to one of five cases, MAFLD does not include lean NAFLD/non-alcoholic steatohepatitis (NASH) and/or genetically determined NAFLD as well as the fact, that steatosis might vanish in the natural course of NAFLD. In fact, in a significant number of patients with NASH and advanced stage fibrosis or cirrhosis, there is no significant steatosis detectable (burnt-out NASH) (6). As the diagnosis of steatosis in NAFLD and MAFLD is solely based on ultrasound, individuals with burnt-out NASH would not be detected in the analysis by Kim et al. This is of particulate interest, since according to a biopsy-based study, advanced fibrosis is the strongest predictor of survival in lean and obese Caucasians with NAFLD (HR =7.4; 95% CI: 1.3–41.3) (7). We and others have previously shown that liver-related and non-liver-related mortality was closely associated with advanced fibrosis and cirrhosis (HR =4.17; 95% CI: 4.09–4.26) (8).

In another study published earlier in 2021, Huang et al. analysed the NHANES-III database for a medium follow-up of 22.8 years (vs. 23 years by Kim et al.) and identified 12,480 individuals that fulfilled their inclusion criteria (vs. 7,761 by Kim et al.), given different inclusion and exclusion criteria (9). Here, in line with previous data and Kim et al., the authors revealed that MAFLD was present in 84% of individuals who met the MAFLD criteria. As previously shown, in this cohort, discordant patients with NAFLD but not MAFLD mostly represented the lean population without metabolic risk factors and with a better outcome. Similarly to Kim et al., diagnosis of steatosis was based on ultrasound assessment as performed according to NHANES study protocol. Fibrosis was again assessed via NFS, APRI and Fib-4. Again, overall-mortality was increased in MAFLD (HR =2.07; 95% CI: 1.86–2.29) while the overall mortality risk in NAFLD was even decreased after adjustment for metabolic risk factors. Given the similarities in methodology, this might again be explained by methodological factors and the applied definition of NAFLD. In fact, in contrast to other liver diseases, NAFLD is a constantly growing driver of global chronic liver disease (CLD) and accounting for 8.9% of DALYs in individuals with cirrhosis in 2017, according to the global burden of disease (GBD) database (10). Interestingly, upon further subgroup analysis, Huang et al. revealed that viral hepatitis and harmful alcohol consumption, which are by definition excluded in NAFLD, were among the strongest predictors of mortality in MAFLD patients.

Taken together, MAFLD might be seen as a group of individuals with metabolic dysfunction comprising a number of different underlying liver diseases and a higher rate of cancer and death as compared to ultrasound-based diagnosis of NAFLD. MAFLD does not include individuals with lean-NASH, a distinct disease entity with increased risk for liver-related mortality, which has not been assessed by Kim et al. Furthermore, the diagnostic criteria for NAFLD applied by Kim et al. were limited by the sonographical presence of steatosis, which might not be present in advanced disease and therefore limit the interpretation of results on all-cause mortality. Last, but not least, from the initial inclusion of patients into the NHANESIII cohort 1988–1994 until the final analysis of mortality data in 2015, clinical knowledge and awareness of NAFLD as a relevant diagnosis has dramatically changed. It might therefore be possible, that study participants, that have been diagnosed with NAFLD received efficient counselling and performed lifestyle modification, which prevented them from any fatal (hepatic and extrahepatic) outcome.

In conclusion, the above-mentioned innovations in nomenclature reveal clinical challenges as well as the awareness of metabolic dysfunction as a relevant, yet modifiable outcome factor. While MAFLD and NAFLD share common features of disease (i.e., steatosis), they are not interchangeable and do not define the same population. As the authors state, further prospective data is needed to better identify individual features and the optimal application of NAFLD vs. MAFLD for the individual patient according to provide a tailored risk assessment strategy and avoid misclassification. Physicians should be encouraged using the new terminology and increase awareness of concomitant metabolic disturbance for providing timely treatment and management of this
preventable disease and its complications.

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